REMARKS/ARGUMENTS

Claims 7-9, 13, 14, and 20-25 remain in this application.

Claims 1-6, 10-12 and 15-18 have been canceled.

Claim 20-25 have been added.

Claim 15-18, withdrawn as the result of an earlier restriction requirement, are canceled without prejudice to the subject matter contained therein. In view of the Examiner's earlier restriction requirement, Applicants retain the right to present claims 15-18 in a divisional application.

In response to the Office Action of April 8, 2004, Applicant requests re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

Obviousness Type Double Patenting

Claims 1-4, 6-9 and 11-14 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of copending Application No. 09/878,115. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons. Claims 1-14 of the `115 application are drawn to unimolecular polymeric micelles comprising an ionizable inner core and a hydrophilic outer shell wherein said ionizable inner core includes ionizable repeating units in

combination with non-ionic hydrophobic repeating units and wherein said ionizable repeating units include at least one compound selected from the group consisting of alkylacrylic acid derivatives, acrylic acid derivatives, aminoalkylacrylate derivatives, and (aminoalkyl) alkylacrylate derivatives, wherein said hydrophobic repeating units include at least one compound selected from the group consisting of acrylate derivatives, acrylamide derivatives, alkylacrylate derivatives, alkylacrylamide derivatives, arylacrylate derivatives and arylacrylamide derivatives; and wherein said hydrophilic outer shell is not cross-linked and originates from functionalized and hydrophilic polymers and includes at least one hydrophilic compound selected from the group consisting of vinyl monomers, vinyl oligomers and vinyl polymers. As such, the claims of the '115 application are deemed to be drawn to species of the instantly claimed genus, and the instant claims are obvious in view of them.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Accordingly, a Terminal Disclaimer is attached hereto which obviates this ground of rejection.

Rejections under 35 USC 112

Claims 1-4, 6-9, and 11-14 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-4, 6-9, and 11-14 have been indicated as being indefinite in their recitation of "water soluble supramolecular self assemblies". As a term of art, the Examiner has alleged that "supramolecular self assemblies" would clearly be understood to comprise any complex of two or more molecules, such that the instant claims would embrace any water soluble complex consisting essentially of at least two of the recited copolymers. However, Applicant is entitled to be his own lexicographer, and at paragraph [0036] the specification states that "[i]n the present invention, the terms "water-soluble self-assemblies" and "micelles" are equally employed although the proposed structures may not necessarily correspond to the true definition of micelles." As a result it is unclear to the Examiner which structures are within the metes and bounds of the claims and which are not. To the extent that it is unclear to the Examiner as to what is the structure of a "water soluble supramolecular self assembly" it is also unclear to the Examiner

as to what is a "core" of such an assembly, as recited in the final clause of the claim.

Written Description

Claims 1-4, 6-9, and 11-14, which have been deemed to be readable upon a genus of water soluble supramolecular self-assemblies of a polyelectrolyte comprising a generic hydrophilic outer shell, and a generic polyelectrolyte core comprising both ionizable and hydrophobic residues, which not only must exhibit the ability to formulate a water soluble supramolecular self assembly, but also be able to trigger a release of a pharmaceutical agent by altering the ionization state of the assembly core, stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was allegedly not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Examiner states that the claimed invention relates to polymeric water soluble supramolecular self assemblies of a polyelectrolyte consisting essentially of diblock, multiblock or random block copolymers comprising a hydrophobic block containing ionizable or charged units, in combination with non-ionic hydrophobic units, wherein a polyelectrolyte segment

comprising non-ionic hydrophobic units forms a core of the assembly. As discussed above, the breadth of the genus of embraced assemblies is deemed by the Examiner to be unclear because the metes and bounds of "water soluble supramolecular self assemblies" are unclear. In one embodiment, the Examiner indicates that the polyelectrolyte core elements can be rendered hydrophobic by counter ion-mediated charge neutralization, thereby allowing micelle formation. The specification teaches that micelles comprising the copolymers may be destabilized by inducing ionization of the hydrophobic polyelectrolyte core, thereby allowing delivery of drugs sequestered therein. The essence of the invention is deemed by the Examiner to be the stabilization of the supramolecular self-assemblies by inclusion of hydrophobic, non-ionizable monomers within the polyelectrolyte portion of the copolymer.

With respect to the issue of a generic water soluble self assembly consisting essentially of a polyelectrolyte, the Examiner indicates that the specification teaches the formation of micelles comprising the recited polyelectrolytes. However, the genus of water soluble self assemblies is alleged by the Examiner to comprise a vast breadth of structures that includes liposomes, hexagonal arrays, and any soluble structure containing two or more of the recited polyelectrolytes. However,

the Examiner goes on to indicate that the specification discloses only the formation of micelles, and lacks any disclosure of any other defined supramolecular self assembly.

With respect to the issue of a generic polyelectrolyte core comprising both ionizable and hydrophobic residues as claimed, the Examiner has acknowledged that the as-filed specification discloses sufficiently an ionizable core composed of ionizable repeating monomers in combination non-ionic hydrophobic repeating monomers, wherein the ionizable repeating monomers include at least one compound selected from the group consisting of alkylacrylic acids and derivatives, aminoalkylacrylates and derivatives, and (aminoalkyl) alkylacrylates and derivatives, and wherein the non-ionic hydrophobic repeating monomers include a hydrophobic vinyl compound. With respect to the issue of a generic hydrophilic outer shell, the Examiner has indicated that the as-filed specification discloses sufficiently a hydrophilic shell composed of functionalized and hydrophilic block-copolymers comprising repeating vinyl monomers. However, the Examiner further indicates that the as-filed specification does not provide sufficient written description of any other representative number of species other than the limited species as indicate above.

The Examiner thus indicates that, in his opinion, the present claims relate to an extremely large number of possible water soluble supramolecular self-assemblies that must exhibit the biological properties as contemplated by the as-filed specification. The as-filed description coupled with the state of the prior art are deemed to provide sufficient description of micelle based block copolymers comprising repeating vinyl monomers on the hydrophilic shell and an ionizable core composed of ionizable repeating monomers alone or in combination with non-ionic hydrophobic repeating monomers, wherein the ionizable repeating monomers include at least one compound selected from the group consisting of alkylacrylic acid derivatives, acrylic acid derivatives, aminoalkylacrylate derivatives, and (aminoalkyl) alkylacrylate derivatives, and wherein the non-ionic hydrophobic repeating monomers include a hydrophobic vinyl compound.

Thus, the Examiner concludes that on the basis of Applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or assays and/or any other unspecified structure containing unspecified compounds that are yet to be discovered but embraced the claimed invention, wherein the

detailed and a substantially and specifically common structure of the genera of the claimed compounds were not described; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structure(s) of component(s) that are linked structurally to the extent that the described structures with essential elements must be able to reflect any of the disclosed biological functions as contemplated by the as-filed specification. The claimed invention as a whole is alleged as not being adequately described if the claims require essential or critical elements which are not adequately described in the specification and which is not conventional in the art as of applicants effective filing date. The Examiner takes the poition that claiming unspecified molecular structures of materials) or claiming compounds without an adequate written description of essential elements of the compounds in order to exhibit applicant's intended claimed property, e.g. trigger a release of a pharmaceutical agent by altering the ionization - state of the micelle core contained within a hydrophilic shell, without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See Fiers v. Revel, 25 USPQ2d 1601 (CA FC 1993) and Regents of the Univ. Calif. v.

Eli Lilly & Co., 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art could recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics. Inc., 48 USPQ2d 1641, 1646 (1998).

Enablement

Claims 1-4, 6-9, and 11-14 stand rejected under 35 U.S.C. 112, first paragraph, because the specification is only deemed to be enabling for claims limited to: micelles consisting essentially of a polyelectrolyte block copolymer comprising at least one ionizable but hydrophobic block composed of ionizable repeating monomers in combination with nonionic hydrophobic repeating monomers, and at least one hydrophilic block, wherein said hydrophilic block comprises a functionalized and hydrophilic polymer comprising repeating vinyl monomers, wherein the ionizable repeating monomers include at least one compound selected from the group consisting of alkylacrylic acid derivatives, acrylic acid derivatives, aminoalkylacrylate derivatives, and (amino alkyl) alkylacrylate derivatives, and wherein the non-ionic hydrophobic repeating monomers include a hydrophobic vinyl compound.

The Examiner takes the position that the claimed invention is not supported by a sufficient written description for possessing of the genus of water soluble supramolecular self-assemblies of a polyelectrolyte.

Furthermore, the Examiner indicates that the state of the prior art exemplified by Benahmed (Pharmaceutical Research, Vol. 18, No. 3, 2001, pp. 323-328) states that polymeric micelles are generally prepared from amphiphilic diblock or multiblock copolymers, that most studies dealt with the preparation or the use of PEG or PVP for the making of a hydrophilic shell, and that hydrophobic vinyl compounds are employed to make a hydrophobic core (page 323, column 1-2). In addition, the Examienr indicates that Jones et al. (European J. of Pharm. Biopharm. 48, 101-11 1, 1999) further states that polymeric micelles are characterized by a core-shell structure, and that pharmaceutical research on polymeric micelles has been mainly focused on copolymers having an A-B diblock structure with A, the hydrophilic shell) and B, the hydrophobic polymers (core, respectively). The presently pending claims are deemed by the Examiner to embrace an enormous number of supramolecular self-assemblies, which are not limited to those stated in the prior art and exemplified in the as-filed specification. Given the state of the prior art, the breadth of the claims, the nature of

the invention, the lack of working examples and/or guidance for the making of unimolecular micelles other than those deemed to be enabling, it is not apparent to the Examiner how a skilled artisan, without any undue experimentation, practices the full scope of the claimed invention as set forth in the claims.

Accordingly, various of the rejected claims have been cancelled, and new claim 20 has been added. Applicant wishes to thank the Examiner for the courtesies extended during a telephone conference on or about Aug. 8, 2004, with the undersigned and Dr. J.C. Leroux (one of the inventors) during which it was determined that the term "multimolecular micelle" was more accurate in describing the instantly claimed compounds.

The term "multimolecular micelle" is understood to mean a composition based on micro and/or nano-associated polyelectrolyte copolymers having a block or graft copolymer architecture consisting of a polyelectrolyte linked to a non-ionic water-soluble polymer.

Examples of multimolecular micelles may include microparticles including microspheres and nanoparticles including nanospheres, and containing

1) a polyelectrolyte copolymer comprising at least one ionizable or charged but hydrophobic block composed of ionizable or charged repeating monomers in combination with

nonionic hydrophobic repeating monomers; and

2) at least one hydrophilic block wherein said hydrophilic block comprises a polyethylene glycol or is synthesized from at least one hydrophilic vinyl monomer;

wherein the ionizable or charged repeating monomers include at least one compound selected from the group consisting of alkylacrylic acid derivatives, acrylic acid derivatives, aminoalkylacrylate derivatives, and (amino alkyl) alkylacrylate derivatives, and wherein the non-ionic hydrophobic repeating monomers include a hydrophobic vinyl compound.

In one embodiment, the polyelectrolyte copolymer is a graft copolymer having grafted hydrophilic and non-ionic oligomers or polymers formed from distinct monomers including at least one ionizable or charged unit composed of ionizable or charged repeating monomers in combination with distinct monomers which include nonionic hydrophobic repeating monomers, wherein said grafted hydrophilic and non-ionic oligomers or polymers are a polyethylene glycol or are synthesized from at least one hydrophilic vinyl monomer, wherein the ionizable or charged repeating units include at least one compound selected from the group consisting of alkylacrylic acid derivatives, acrylic acid derivatives, aminoalkylacrylate derivatives, and (amino alkyl) alkylacrylate derivatives, and wherein the non-ionic hydrophobic

repeating units include a hydrophobic vinyl compound.

Basis for these remarks may be found with reference to the specification at page 1, lines 12-20; page 6, line 16 of the background to the invention; "PICM have a block or graft copolymer architecture and consist of a polyelectrolyte linked to a non-ionic water-soluble polymer"; also see page 7, lines 10-12 wherein are mentioned multiblock copolymers and ionizable and permanently-charged random copolymers with grafted hydrophilic and essentially non-ionic oligomers.

With regard to claim 13, the inclusion of ethylene oxide and ethylene glycol, this is derived from the specification at page 3 line 6 of the background to the invention which states;' Multiblock copolymers such as poly(ethylene oxide)-poly(propylene oxide) etc. ----- can also self organize into micelles.' One skilled in the art understands tha ethylene oxide is required to make poly(ethylene oxide). Likewise, with regard ethylene glycol, see numerous portions of the specification, e.g. Figures 2-4, Table 1 and various of the examples.

Rejections under 35 USC 102(b)

Claims 1 and 14 stand rejected under 35 U.S.C. 102(b) as being anticipated by Heller et al (J. Pharm. Sci. 88(1): 58-64,

1999) as evidenced by Stryer (In Biochemistry, Fourth edition, W.H. Freeman and Co., New York), GenBank Accession No. AAA21101, published 8/6/1994) and GenBank Accession No. CAA23748, published 4/24/1993).

Heller teaches polyethylene glycol (PEG) modified hemoglobin. Stryer teaches that human hemoglobin is a four subunit protein composed of 2 alpha globin and 2 beta globin subunits. See pages 154 and 155. GenBank Accession No. AAA21101 shows that human beta globin comprises both hydrophobic and ionizable monomers, e.g. the first 10 amino acids include four hydrophobic residues (M, V, L, and P), and 4 ionizable residues (H, E, E, and K). GenBank Accession No. CAA23748 shows that human alpha globin comprises both hydrophobic and ionizable monomers, e.g. the first 10 amino acids include four hydrophobic residues (M, V, L, and P), and 2 ionizable residues (D and K). As such, Heller is deemed to teach a water soluble supramolecular assembly of a polyelectrolyte. The composition can be considered to be a random copolymer with grafted hydrophilic, nonionic PEG groups. The composition can be considered to comprise a pharmaceutical constituent, which is a drug, i.e. the iron atoms in the heme porphyrins.

As instantly presented, the claims are now deemed to preclude the composition of Heller, and therefore this ground of

rejection is respectfully deemed to be moot.

SUMMARY

In light of the foregoing remarks and amendment to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,

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